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Radiation crosslinked psyllium and polyacrylic acid based hydrogels for use in colon specific drug delivery

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Abstract

In order to utilize the psyllium husk, a medicinally important natural polysaccharide, to develop the hydrogels meant for the drug delivery, we have prepared psyllium and polyacrylic acid based polymeric networks by radiation-induced crosslinked copolymerization. Polymeric networks (hydrogels) thus formed were characterized with SEMs, FTIR and swelling studies. Swelling behavior of the hydrogels was studied as a function of monomer concentration in the hydrogels and temperature, pH and [NaCl] of the swelling medium. This paper discusses the swelling kinetics of the hydrogels and release dynamics of anticancer model drug 5-fluorouracil from the hydrogels for the evaluation of swelling and drug release mechanisms. It has been observed from the release dynamics of drug that diffusion exponent 'n' have 0.7, 0.8 and 0.7 values and gel characteristics constant 'k' have 9.13×10^{-3}, 6.22×10^{-3} and 9.01×10^{-3} values for the release of 5-fluorouracil, respectively, in distilled water, pH 2.2 buffer and pH 7.4 buffer. The values of the diffusion exponent show that the release of drug from drug-loaded hydrogels has occurred through Non-Fickian diffusion mechanism. It has also been observed from the swelling and release of drug in the different pH buffer that the polymer matrix is pH responsive and can be exploited for the delivery of anticancer drug to the colon.

Keywords: Copolymerization; Drug delivery; pH responsive hydrogels; Functionalization; Psyllium

1. Introduction

Grafting and crosslinking are common practice to improve the functional properties of polysaccharides and are carried out by chemical initiation (Mostafa & Morsy, 2004) or radiation initiation polymerization (Karadag, Saraydin, & Güven, 2001; Saraydin, Karadag, & Güven, 1997, 1995a, 1995b). In case of chemical initiated copolymerization, sometime initiator and crosslinking agent left in the polymeric networks which affect structural homogeneity, swelling behavior and mechanical properties of the hydrogels. In order to prepare the hydrogels for technological important applications the network should be free from these impurities. This can be achieved by synthesizing the polymers through irradiation-induced copolymerization (Rosiak, Burczak, Czolozynska, & Pekala, 1983). Graft copolymerization of vinyl monomers onto polysaccharides has been carried out by a simultaneous irradiation technique using gamma-rays as the initiator (Abdel-Aal, Gad, & Dessouki, 2006) and reaction has been controlled by incorporating a homopolymer-inhibiting agents (Khan, 2005). Percentage grafting increases with increase in the monomer concentration and total dose (Huang, Shen, Sheng, & Fang, 2005) and it affects the mechanical and thermal properties of the polymers. El-Hag Ali and coworkers have carried out the acrylic acid/vinyl sulfonic acid based copolymerization by using γ-radiation and have observed that the comonomer composition and irradiation dose affects the swelling property of the hydrogels (El-Hag Ali, Abd El-Rehim, Hegazy El-Sayed, & Ghobashy, 2006). The hydrogels prepared by the irradiation have been used to study the release of anticancer drug and diffusion of 5-fluorouracil (5-FU) solution from the hydrogels has been found the

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Non-Fickian type (Taşdelen, Kayaman-Apohan, Güven, & Baysal, 2005). The in vitro release dynamics of the drug from the hydrogels is not only dependent upon the extent of crosslinking, but also on the amount of drug loaded, method of drug loading and pH of the release medium (Soppimath, Kulkarni, & Aminabhavi, 2000; Soppimath & Aminabhavi, 2002).

Cancer of the colon is a major health problem which can develop with other conditions, such as ulcerative colitis, a chronic inflammation in the colon. Diets that include wheat bran in combination with psyllium is an effective means of reducing colon cancer risk in human populations addicted to high-risk western diets (Alabaster, Tang, Frost, & Shivapurkar, 1993, 1996). The presence of *n*-butyrate in the distal colon may be important in the prevention of colon cancer because the majority of tumors in both human and experimentally induced rodent cancer models occur in the distal colon (Bufill, 1990; Holt, Mokulo, Distler, Liu, & Reddy, 1996). *n*-Butyrate possesses anti-neoplastic effects in human colon carcinoma cells and it exerts a concentration-dependent slowing of the rate of cancer cell proliferation and promotes expression of differentiation markers in vitro (Kim et al., 1980; Whitehead, Young, & Bhathal, 1986), and leading to reversion of cells from a neoplastic to a nonneoplastic phenotype (Wilson, 1989). Also, fecal *n*-butyrate concentration of patients with colorectal cancer has been reported to be lower than those of healthy controls (Weaver, Krause, Miller, & Wolin, 1988). The end products of microbial carbohydrate fermentation in the large bowel include short-chain fatty acids (SCFA), among which acetate, propionate and *n*-butyrate are quantitatively most important (Cummings, 1981; Cummings, Beatty, Kingman, Bingham, & Englyst, 1996, 1987; Pouillart, 1998). Psyllium delayed the fermentation rate of high amylose cornstarch in the cecum and shifts the fermentation site of starch toward the distal colon, leading to the higher *n*-butyrate concentration in the distal colon and feces (Morita et al., 1998, Morita, Kasaoka, Hase, & Kiriyama, 1999). Beside its cancer lowering property it has been reported for the treatment of constipation, diabetes, diarrhea, inflammation bowel diseases-ulcerative colitis, obesity in children and adolescents and high cholesterol (Singh, 2007). Psyllium mucilage obtained from the seed coat by mechanical milling/grinding of the outer layer of the seeds and yield amounts to approximately 25% of the total seeds yield. Mucilage is fibrous, hydrophilic and forms the clear colorless mucilaginous gel by absorbing water. Gel-forming fraction of the alkali-extractable polysaccharides composed of arabinose, xylose and traces of other sugars (Fischer, Nanxiong, Ralph, Andersond, & Marletta, 2004).

Keeping in view, the pharmacological importance of psyllium polysaccharides and drug delivery devices based on hydrogels, psyllium, if suitably tailored to prepare the hydrogels, can act as the double potential candidates for the novel drug delivery systems. Therefore, the present study is an attempt, to synthesize psyllium and poly(-AAc) based hydrogels by using radiation-induced cross-linked polymerization and thereafter use as drug delivery devices. Polymeric networks thus formed have been characterized with SEMs, FTIR and swelling studies. Swelling behavior of the hydrogels has been studied as a function of monomer concentration in the hydrogel and temperature, pH and [NaCl] of the swelling medium. This paper discusses the swelling kinetics of the hydrogels and release dynamics of anticancer model drug 5-fluorouracil from the hydrogels for the evaluation of swelling and drug release mechanism from the polymer matrix.

2. Experimental

2.1. Materials and methods

Plantago psyllium mucilage (Psy) was obtained from Sidpur Sat Isabgol factory (Gujarat, India), acrylic acid was obtained from Merck-Schuchardt, Germany. 5-Fluorouracil was procured from Dabur India Ltd.

2.2. Synthesis of psy-cl-poly(AAc)

Reaction was carried out with 1 g psyllium husk and definite concentration of acrylic acid in a test tube. The reaction mixture was irradiated with gamma rays from ^{60}Co gamma chamber for 24 h with total dose of 58.32 kGy. Polymers thus formed were named as psy-*cl*-poly(AAc) and were stirred in distilled water and ethanol for 1 h each to remove the soluble fraction and then were dried in an oven at 40 °C. The optimum reaction parameters were evaluated for the synthesis of psy-*cl*-poly(AAc) by varying the monomer concentration from 2.91×10^{-1} to 14.55×10^{-1} mol/L on the basis of swelling and surface consistency of the polymer after 24 h in distilled water at 37 °C.

2.3. Characterization

Polymers were characterized by SEMs, FTIR spectroscopy and swelling studies. SEMs were taken on Jeol Steroscan 150 Microscope and FTIR spectra of polymers were recorded in KBr pellets on Nicolet 5700FTIR THERMO.

2.4. Swelling kinetics

Swelling kinetics of the polymeric networks was carried out in triplicate by gravimetric method. Known weight of polymers were taken and immersed in excess of water for different time intervals at 37 °C and then polymers were removed, wiped with tissue paper to remove excess of solvent, and weighed immediately. The difference in weight has given the amount of water uptake by the polymers after definite time intervals.